Cost-Effectiveness of intensive lipid lowering therapy with 80 mg of atorvastatin, versus 10 mg of atorvastatin, for secondary prevention of cardiovascular disease in Canada

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COST- EFFECTIVENESS OF INTENSIVE LIPID LOWERING THERAPY WITH 80 MG OF ATORVASTATIN, VERSUS 10 MG OF ATORVASTATIN, FOR SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE IN CANADA

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ABSTRACT

Background
The TNT study compared high dose atorvastatin (80 mg) versus moderate atorvastatin (10 mg) treatment in 10,001 patients with stable coronary heart disease (CHD), over 4.9 years. Intensive lipid-lowering with atorvastatin (80 mg) reduced major cardiovascular events by 22%.

Objectives
To assess the cost-effectiveness of intensive lipid-lowering versus moderate lipid lowering treatment from the perspective of the Canadian Ministries of Health.

Methods
A lifetime Markov model was developed to predict cardiovascular (CV) events, costs, survival, and quality-adjusted life years (QALYs) for CHD patients receiving 80 mg versus 10 mg of atorvastatin. Predictions were also made for 10- and 5-year horizons. Treatment-specific event risks were used until five years. Beyond year five, equivalent CV risks were assumed for all patients. Medical-care costs and post-event survival were estimated using Canadian data. Health utility scores were obtained from published studies. Benefits and costs were discounted 5% annually. Probabilistic and deterministic sensitivity analyses were performed.

Results
Treatment with atorvastatin (80 mg) over a lifetime horizon resulted in increased costs (Can$16,542 vs. Can$15,365), survival (10.12 vs. 10.03 life years), and QALYs (7.71 vs. 7.61) per patient compared with atorvastatin (10 mg), yielding an incremental cost-effectiveness of Can$12,946 per life year gained and Can$11,969 per QALY. The incremental cost per QALY remained below Can$50,000 in 98.1% of 1000 simulations. Results were robust to variations in event hazard ratios, costs, health utility values, and discount rate.

Conclusion
Intensive atorvastatin (80 mg) treatment is predicted to be cost-effective versus atorvastatin (10 mg) for CHD patients in Canada.

Key words: *Cardiovascular disease, atorvastatin, Markov model, cost-effectiveness, Canada*

Cardiovascular disease (CVD) is the leading cause of death in Canada accounting for 30% of all deaths in 2004.[1] CVD was responsible for 18% of all hospitalizations in 2001.[2] CVD also severely impacts a patient's quality of life. In the Canadian Community Health Survey (2000-2001), 14% of men and 21% of women diagnosed with CVD reported difficulty walking.[3] This

survey also showed that a total of 2.8 years of health-adjusted life expectancy (i.e., life expectancy modified by a health utility score to give equivalent years of good health) and 4.5 years of life expectancy were lost due to CVD.[3]

The total annual cost of CVD in Canada was estimated to be Can$20.1 billion annually in 2000.[4] This includes both direct costs of treatment and hospitalization and indirect costs such as the loss of productivity due to premature mortality. According to Health Canada's Economic Burden of Illness in Canada (1998)[5] report, CVD was the most costly diagnostic category of disease in Canada, with total costs for CVD accounting for 11.6% (Can$18.5 billion) of the total cost of illness in 1998. From 1992 to 2002, annual expenditure for the management of ischemic heart disease nearly doubled and total expenditure exceeded Can$2.8 billion over the 10-year period.[6]

Prevention of major cardiovascular (CV) events by lowering low-density lipoprotein cholesterol (LDL-C), using either diet or medication, is a well known treatment strategy.[7] A recent meta-analysis of 62 studies (216,616 patients) including 24 randomized controlled trials (126,474 patients) by Gould et al.[8] found that for every mmol/L reduction in LDL-C there was a 28.0% reduction in the relative risk of coronary heart disease (CHD)-related mortality and a 26.6% relative risk reduction of CHD events. Similarly, a previous meta-analysis of 14 randomized clinical trials by Baigent et al.[9] showed that incidence of major coronary events, stroke, and revascularization procedures was reduced by one fifth, over a 5-year period, for every mmol/L reduction in LDL-C, regardless of the baseline LDL-C levels. Intensive statin therapy to lower LDL-C levels further than the previously recommended guideline of 2.59 mmol/L for patients with CHD has been the subject of recent studies,[10,11] including the Treat to New Targets (TNT) study.[12] Canadian Cardiovascular Society guidelines from 2006 now recommend lowering LDL-C below 2.0 mmol/L in high-risk patients with pre-existing CHD.[13]

The TNT study[12] was a prospective, double-blind, randomized, controlled trial that compared intensive lipid-lowering with 80 mg of atorvastatin per day to moderate lipid lowering with 10 mg of atorvastatin per day in patients with pre-existing CHD. Patients with clinically evident CHD-defined by the presence of previous myocardial infarction (MI), a history of coronary revascularization, or previous or current angina-were recruited in 14 countries (1052 subjects were randomized from Canadian sites). The patients, 10,001 in all, were followed for a median of 4.9 years.

LDL-C levels were reduced to a mean value of 2.0 mmol/L for patients receiving 80 mg atorvastatin, compared to 2.6 mmol/L for patients receiving 10 mg.[12] Patients receiving the 80 mg daily dose of atorvastatin experienced a 22% relative reduction (hazard ratio [HR]:0.78; 95% confidence interval [CI]: 0.69 to 0.89; $P<.001$) in the rate of major CV events, which included death from CHD, non-fatal non-procedure-related MI, resuscitation after cardiac arrest (RCA), and fatal or nonfatal stroke. There was no difference between the two groups for overall mortality.

Previous studies of the cost-effectiveness of statin treatment in Canada have compared treatments with different statins[14] or statin treatment with no treatment.[15-17] It is currently unknown whether intensive lipid-lowering with a higher and more expensive atorvastatin dose is cost-effective versus moderate lipid lowering with a lower atorvastatin dose in the Canadian context. Therefore, the objective of this study was to assess the cost-effectiveness of intensive lipid-lowering for patients with stable CHD treated with 80 mg of atorvastatin per day versus 10 mg of atorvastatin per day based on the results of the TNT study from the perspective of the Canadian Ministries of Health.

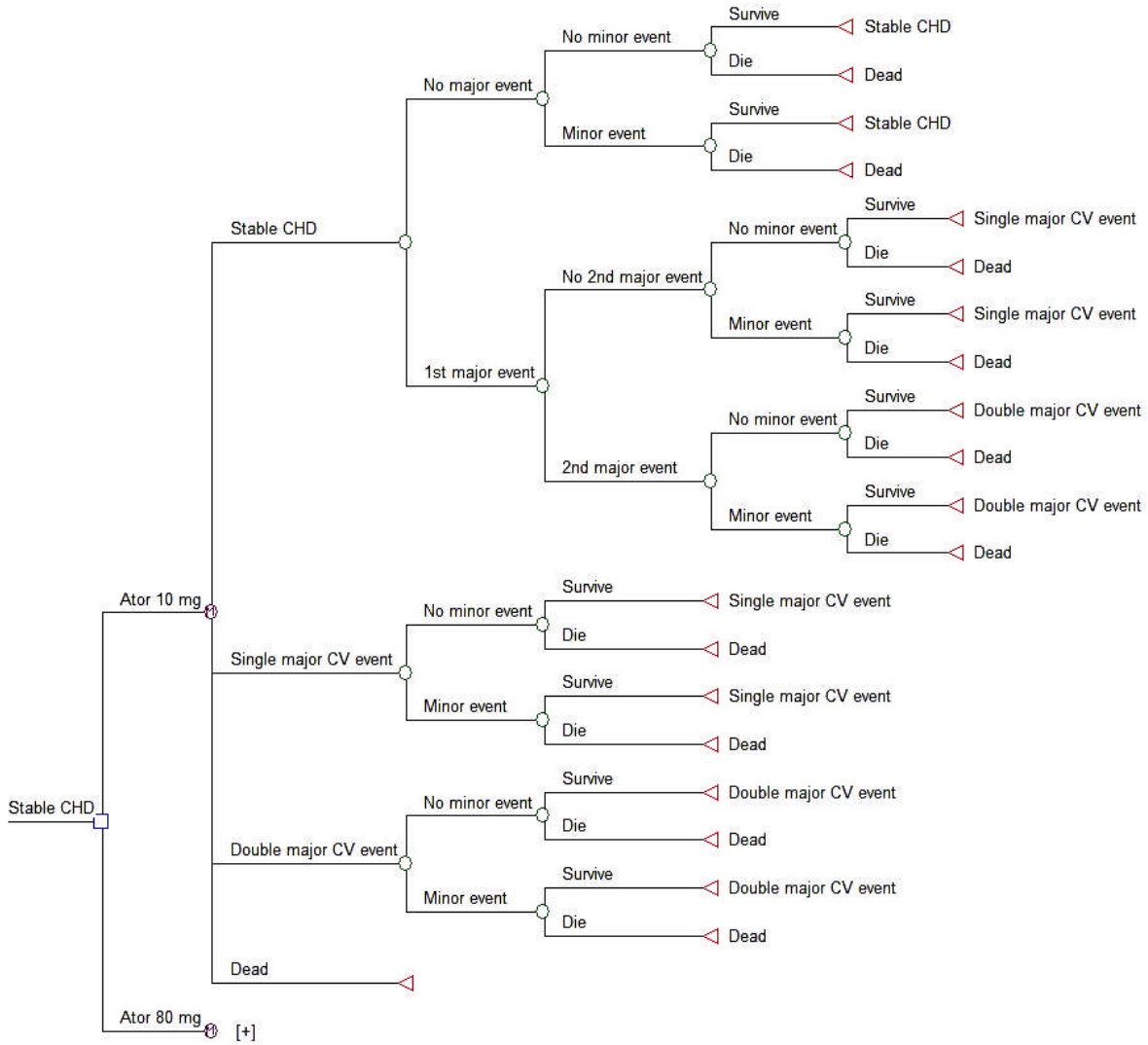
METHODS

Model Design

A Markov model with a lifetime horizon was developed to predict major and minor CV events, survival, costs, and quality-adjusted life years (QALYs) in the Canadian context for CHD patients treated with 80 mg versus 10 mg of atorvastatin (Figure 1). Predictions for 5- and 10-year model horizons were also made; patients were assumed to continue with their original atorvastatin dosages throughout the model. The model comprises four health states: Stable CHD, Single Major CV event, Double Major CV event, or Death. All patients enter the model in the

'Stable CHD' state. During each 1-year cycle, patients can suffer a single (first) major CV event resulting in a transition to the 'Single Major CV event' state or suffer two major CV events within the same year and transition to the 'Double Major CV event' state. Patients may also remain in their respective health states or die from any cause. A major CV event was defined as MI, stroke, congestive heart failure (CHF), RCA, or revascularization either by coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). A minor CV event, defined as peripheral artery disease, transient ischemic attack, or documented angina, can occur at any point but will not cause transition of the patient to a different health state.

FIG. 1 State-transition model for 80 mg of atorvastatin per day versus 10 mg of atorvastatin per day. CHD: coronary heart disease



Patient Population

The patient population in the model was assumed to have similar characteristics as patients enrolled in the TNT study;[12] i.e., a mean age of 61 years, with 18% being aged 70 or older, and 81% males.

Model Input Parameters

Annual event probabilities and hazard ratios were based on TNT trial data (Table 1). First CV event risks were treatment-specific for the first five years, and these treatment specific five-year event risks were extrapolated to ten years. Based on the results of two long-term follow-up studies of statin outcome trials,[18,19] we assumed that the event rates were constant over time between 5- and 10-years. After year 10, it was assumed that the major and minor CV event rate was equal in both treatment strategies. Probabilities for second events were not treatment-specific as rates were reported to be similar across treatment groups, and were based on TNT trial data pooled for patients receiving 10 mg and 80 mg atorvastatin (Table 1).[12] RCA events were not considered in the second event analyses due to the low number of events (51) observed in the TNT trial.

The base-case scenario assumed no differences in event specific mortality between 10 mg and 80 mg atorvastatin since the TNT study was not powered to detect differences in mortality between treatment groups. Patients who did not experience a major CV event ('Stable CHD' state) were assigned an all-cause mortality rate corrected for CHD mortality by subtracting deaths due to acute MI, cerebrovascular diseases and CHF (non-CHD mortality) (Table 2).[20] Non-CHD mortality rates were multiplied by a factor of 2 (mortality multiplier)[21] to account for the elevated mortality in patients with stable CHD compared to the general population (Table 2).

TABLE 1 Model input parameters: annual event probabilities

Clinical event probabilities (per year)	10 mg Atorvastatin (Year 1–10)	80 mg Atorvastatin (Range for DSA) (Year 1–10)	Pooled 10 mg and 80 mg atorvastatin (Year 10+)
Initial events			
Myocardial infarction	0.0123	0.0094 (0.0075–0.0113)	0.0102
Stroke	0.0055	0.0043 (0.0029–0.0057)	0.0049
Chronic heart failure	0.0055	0.0037 (0.0025–0.0049)	0.0046
Revascularization	0.0350	0.0254 (0.0224–0.0283)	0.0302
Resuscitated cardiac arrest	0.0008	0.0009 (0.0001–0.0016)	0.0009
Peripheral artery disease	0.0108	0.0106 (0.0084–0.0127)	na
Transient ischemic attack	0.0041	0.0033 (0.0021–0.0046)	na
Documented angina	0.0264	0.0233 (0.0204–0.0264)	na
Subsequent events (occurring within 1 year of first event)*			
Myocardial infarction followed by			
Myocardial infarction			0.0489
Stroke			0.0147
Chronic heart failure			0.0440
Revascularization			0.3961

Stroke followed by	
Myocardial infarction	0.0191
Stroke	0.0813
Chronic heart failure	0.0048
Revascularization	0.0335
Congestive heart failure followed by	
Myocardial infarction	0.0452
Stroke	0.0101
Chronic heart failure	0.1759
Revascularization	0.0955
Revascularization followed by	
Myocardial infarction	0.0270
Stroke	0.0105
Chronic heart failure	0.0135
Revascularization	0.1349

*same for all model cycles; DSA: Deterministic sensitivity analysis; na: not available. Source: TNT trial data

TABLE 2 Model input parameters: annual event probabilities

Base-case mortality (per year)	Mortality rates (±SD)	Range for DSA		Source
		High	Low	
All-cause mortality	Population-based age- and sex-specific mortality	n/a	n/a	Statistics Canada[20]
Non-CHD mortality	Population-based age- and sex-specific mortality	n/a	n/a	Statistics Canada[20]
Mortality rates applied for the first year after major event (per year)				
Myocardial infarction	Event-, age- and sex-specific mortality	+/-10% across whole survival curve		Johansen, 2002[22]
Stroke	Event-, age- and sex-specific mortality	+/-10% across whole survival curve		Holroyd-Leduc, 2000[23]
Congestive heart failure	Event-, age- and sex-specific mortality	+/-10% across whole survival curve		Jong, 2002[24]
Revascularization	Event-, and age- specific mortality weighted by the proportion of CABG /PTCA	+/-10% across whole survival curve		Graham, 2002;[25] CCNO[26]
Resuscitated cardiac arrest	0.855	n/a		Gwinnutt, 2000[27]
Mortality multiplier				
Stable CHD	2.0 (±0.306)	2.61	1.39	Lampe, 2000[21]
Myocardial infarction	3.7 (±0.510)	4.72	2.68	Lampe, 2000[21]
Stroke	2.1 (±0.326)	2.75	1.45	Dennis, 1993[28]
Congestive heart failure	2.3 (±0.449)	3.20	1.41	Mosterd, 2001[29]
Revascularization	2.0 (±0.306)	2.61	1.39	same as for stable CHD
Resuscitated cardiac arrest	3.7 (±0.510)	4.72	2.67	same as for MI

n/a: not applicable; CCNO: Cardiac Care Network of Ontario; DSA: Deterministic sensitivity analysis; SD: standard deviation

Patients who experienced a major event (i.e., MI, stroke, CHF, revascularization or resuscitated cardiac arrest) were assigned event-specific mortality rates for the first year post-event. For patients experiencing a second major event during the same model cycle, the mortality rate of the first event was applied. Minor events were assumed not to affect mortality.

For MI,[22] stroke,[23] and CHF,[24] first-year post-event mortality rates by age and sex were estimated from Canadian literature values using a best-fit algorithm (exponential interpolation) and weighted by the proportion of males to females in the model cohort. First-year post-event mortality for revascularization was estimated from Canadian literature values, for each age range[25] and weighted by the current Canadian values for the relative proportion of revascularization procedures (CABG vs. PCI).[26] For resuscitated cardiac arrest, first-year post-event mortality was based on a UK study.[27] Patients who survived a major event beyond the first year were assumed to remain at higher mortality risk than patients with stable CHD to account for the higher risk of death for patients with a history of major CV events compared to the general population.[21,28,29] All-cause mortality rates applied to patients surviving the first year after a major event were based on Canadian population data,[20] and multiplied by event-specific mortality multipliers for the remaining model cycles (Table 2). In the case of patients surviving two major events in one model cycle (i.e., 1-year), the mortality multiplier of the more severe event was used.

Costing and Utilities

Acute event costs, both for major and minor events, were based on the Ontario Case Costing Initiative (OCCI) 2006-2007 acute inpatient cost data (Table 3).[30] Each acute event cost was defined as the total cost of hospitalization due to that event, including overhead. The OCCI database presents both direct and indirect costs of hospitalization, and average length of stay in hospital, for subcategories of each ICD10-CA (International Classification of Diseases, tenth revision, enhanced for Canada) diagnostic category, or Canadian Classification of Health Interventions (CCI) category. Costs were weighted by the number of patients in each of the subcategories resulting in a weighted average of the total hospital cost per day (indirect and direct costs); a weighted average of the length of hospital stay for each diagnostic category (MI, stroke, CHF, RCA, or revascularization (CABG or PCI), peripheral artery disease, transient ischemic attack, or documented angina) was also calculated. Total cost of hospitalization for each event was then calculated by multiplying the total hospital cost per day by the length of hospital stay. Atorvastatin costs were based on the 2007 Ontario Drug Benefit formulary.[31]

Health utility scores were obtained from Sullivan et al.[32] (Table 4). It was assumed that Canadian and US patients have similar utilities. Benefits and costs were discounted at 5% annually, as recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines.[33]

TABLE 3 Model input parameters: annual event probabilities

Costs (Can$2007)	Base-case	Range for DSA		Source
		High	Low	
Atorvastatin Drug Costs				
10 mg atorvastatin	$607.36	$759.72	$455.83	Ontario Drug Benefit formulary[31]
80 mg atorvastatin	$816.14	$1,020.87	$612.52	Ontario Drug Benefit formulary[31]
Major Events				
Myocardial infarction event	$10,578	$13,222	$7,933	Ontario Case Costing Initiative[30]
Stroke event	$17,854	$22,317	$13,390	Ontario Case Costing Initiative[30]
Congestive heart failure event	$10,565	$13,207	$7,924	Ontario Case Costing Initiative[30]
Revascularization event (weighted average)	$12,758	$15,948	$9,569	
Coronary artery bypass graft (CABG)	$23,411			Ontario Case Costing Initiative[30]

Percutaneous transluminal coronary angioplasty (PTCA)	$9,015			Ontario Case Costing Initiative[30]
Resuscitated cardiac arrest	$20,640	$25,800	$15,480	Ontario Case Costing Initiative[30]
Minor Events				
Peripheral artery disease event	$15,366	$19,207	$11,524	Ontario Case Costing Initiative[30]
Transient ischemic attack event	$4,010	$5,013	$3,008	Ontario Case Costing Initiative[30]
Documented angina event	$4,046	$5,057	$3,038	Ontario Case Costing Initiative[30]
Revascularization Weights				
CABG (weight)	0.26	0.3	0.2	Cardiac Care Network of Ontario[26]
PCI (weight)	0.74	n/a	n/a	Cardiac Care Network of Ontario[26]

*total costs (direct plus overhead). DSA: Deterministic sensitivity analysis

TABLE 4 Base-case model input parameters: utilities

	Base-case	Range for DSA	
		High	Low
Stable coronary heart disease utility (baseline)	0.778	0.895	0.661
Utility Decrements			
Myocardial infarction	-0.127	-0.108	-0.147
Stroke	-0.139	-0.118	-0.160
Congestive heart failure	-0.147	-0.125	-0.169
Coronary artery bypass graft – 1st year*	0	-0.075	+0.075
Coronary artery bypass graft – post 1st year*	0	-0.075	+0.075
Percutaneous coronary intervention – 1st year*	0	-0.075	+0.075
Percutaneous coronary intervention – post 1st year*	0	-0.075	+0.075
Resuscitated cardiac arrest	-0.101	-0.086	-0.116
Myocardial infarction and stroke	-0.166	n/a	n/a
Myocardial infarction and CHF	-0.174	n/a	n/a
Myocardial infarction and revascularization	-0.127	n/a	n/a
Stroke and CHF	-0.186	n/a	n/a
Stroke and revascularization	-0.139	n/a	n/a
CHF and revascularization	-0.147	n/a	n/a
Peripheral artery disease	-0.104	-0.088	-0.119
Transient ischemic attack	-0.121	-0.103	-0.140
Documented angina	-0.117	-0.100	-0.135

*In the base-case assumed to be the same value as for stable coronary heart disease. DSA: Deterministic sensitivity analysis; n/a: not applicable. Source: Sullivan, 2005[32]

Sensitivity Analyses

Impact of the uncertainty of model input parameters on the lifetime cost-utility of atorvastatin 80 mg versus 10 mg was assessed using deterministic and probabilistic sensitivity analyses. A more conservative assumption was made by limiting treatment specific event rates to the first five years of the model, the extent of the TNT trial. Subsequent (after 5 years) CV event risks were based on TNT data pooled across the doses. For the deterministic sensitivity analysis, hazard ratios for the 80 mg atorvastatin dose were varied around their base-case values for MI, stroke, revascularization, resuscitation after cardiac arrest, CHF, peripheral artery disease, transient ischemic attack, and documented angina by plus and minus two standard errors (SE) (Table 1). Mortality multipliers (+/- 2 SE) (Table 2), event costs (+/- 25%) (Table 3), stable CHD baseline utility (+/- 15%) and utility decrements (+/- 15%) (Table 4) were also varied around their base-case values. Discount rate was assessed at 0% and 3%. The proportion of revascularizations that are CABG (CABG weight) was also varied

between 0.2 and 0.3 (Table 3). Age, gender, and event specific mortality rates for the year following a CHD event were also varied, by +/- 10%. For the probabilistic sensitivity analysis, event costs (standard deviation [SD]=15% of mean) and mortality multipliers (for SDs, see Table 2) were varied assuming Gamma distributions; utilities (SD=15% of mean) and CABG weight (SD=15% of mean) were varied assuming Beta distributions. Trial-based event probabilities, mortality rates and hazard ratios were varied using non-parametric bootstrapping.

Values for each of these parameters were randomly drawn 1000 times and the aggregate costs and QALYs recalculated at each step yielding a 95% confidence interval for the incremental cost-effectiveness ratio (ICER). Results are presented on a cost-effectiveness plane and as a cost-effectiveness acceptability curve indicating the probability of atorvastatin 80-mg being cost-effective as a function of the societal willingness to pay for a QALY gained.

RESULTS

Over a lifetime horizon, 0.073 fewer CV events per patient were predicted to occur for patients treated with 80 mg of atorvastatin compared to those treated with 10 mg (Table 5). Patients in the 80 mg arm of the model were projected to live 0.091 years longer and have 0.098 more QALYs. Total lifetime costs, including drug costs and the costs of major and minor events, were Can$16,542 per patient treated with 80 mg of atorvastatin and Can$15,365 for patients treated with 10 mg. The incremental drug costs of atorvastatin 80 mg were Can$2,169 per patient, of which a predicted 46% was offset by cost savings resulting from the reduced number of major and minor events in that arm. This resulted in an overall cost difference of Can$1,177 per patient. The incremental cost per QALY gained for 80 mg of atorvastatin versus 10 mg was Can$11,969 (95% CI 5,469 to 40,531) and the incremental cost per year of life gained (LYG) was Can$12,946.

The ICER decreased to Can$6,978/QALY for the 10-year model horizon (Table 5) and Can$5,128/QALY for the 5-year time horizon. For the 10-year horizon, the cost savings stemming from the reduced number of major and minor events in the 80 mg atorvastatin arm rose to offset 79% of the incremental drug costs.

TABLE 5 Base-case Results

	Atorvastatin 80 mg	Atorvastatin 10 mg	Difference
Lifetime horizon			
Number of major CHD events			
Myocardial infarction	0.128	0.140	-0.013
Stroke	0.060	0.064	-0.004
Congestive heart failure	0.062	0.073	-0.011
Revascularization	0.388	0.435	-0.046
Resuscitated cardiac arrest	0.010	0.009	0.001
Total	0.648	0.721	-0.073
Life years	10.116	10.025	0.091
QALYs	7.710	7.611	0.098
Costs (2007 Can$)			
Study drugs	8,262	6,093	2,169
Major events	5,518	6,402	-884
Minor events	2,761	2,869	-108
Total	16,542	15,365	1,177
Incremental cost per event averted (2007 Can$)	16,171		
Incremental cost per life-year gained (2007 Can$)	12,946		
Incremental cost per QALY (2007 Can$) [95% CI]	11,969 [5,469 to 40,531]		
10-year horizon			
Number of major CHD events			

Cost-effectiveness of intensive lipid lowering therapy with 80mg of atorvastatin, versus 10mg of atorvastatin, for secondary prevention of cardiovascular disease in Canada

Myocardial infarction	0.082	0.101	-0.019
Stroke	0.038	0.045	-0.008
Congestive heart failure	0.038	0.053	-0.014
Revascularization	0.242	0.310	-0.068
Resuscitated cardiac arrest	0.007	0.006	0.001
Total	0.407	0.514	-0.108
Life years	7.273	7.240	0.034
QALYs	5.568	5.521	0.047
Costs (2007 Can$)			
Study drugs	5,940	4,400	1,540
Major events	4,103	5,192	-1,089
Minor events	1,885	2,010	-125
Total	11,928	11,601	327
Incremental cost per event averted (2007 Can$)	3,032		
Incremental cost per life-year gained (2007 Can$)	9,682		
Incremental cost per QALY (2007 Can$) [95% CI]	6,978 [dominant to 27,709]		
5-year horizon			
Number of major CHD events			
Myocardial infarction	0.048	0.061	-0.013
Stroke	0.022	0.027	-0.005
Congestive heart failure	0.022	0.032	-0.009
Revascularization	0.142	0.187	-0.045
Resuscitated cardiac arrest	0.004	0.004	0.000
Total	0.238	0.311	-0.073
Life years	4.561	4.550	0.011
QALYs	3.507	3.489	0.018
Costs (2007 Can$)			
Study drugs	3,725	2,765	960
Major events	2,636	3,427	-791
Minor events	1,123	1,200	-77
Total costs	7,484	7,392	92
Incremental cost per event averted (2007 Can$)	1,260		
Incremental cost per life-year gained (2007 Can$)	8,241		
Incremental cost per QALY (2007 Can$) [95% CI]	5,128 [dominant to 32,902]		

CHC: coronary heart disease; QALY: quality-adjusted life year; CI: confidence interval

Sensitivity Analyses

Sensitivity analysis was conducted using a more conservative assumption with respect to event rates. In this case, treatment specific event rates were limited to the first five years of the model, the extent of the TNT trial. After 5 years, CV event risks were based on TNT data pooled across the doses. This resulted in a cost per life year saved of Can$25,406 and an ICER of Can$22,457/QALY (95% CI: 12,994–72,479).

Deterministic sensitivity analysis for the lifetime horizon showed that the model was moderately sensitive to variations in the hazard ratios for atorvastatin 80 mg versus 10 mg with respect to MI, minor events, revascularization, resuscitation after cardiac arrest, stroke and CHF (Figure 2). The maximum ICER (Can$19,570/QALY) was obtained when the hazard ratio for MI was increased from the base-case value of 0.765 to 0.920 (+2 SE); the minimum ICER (Can$8,205/QALY) when the hazard ratio for MI was decreased from the base-case value of 0.765 to 0.610 (-2 SE). Event utility decrements were varied about the base-case value by plus or minus 15 percent giving a maximum ICER of Can$16,859/QALY (with reduced event utility decrements) and a minimum of Can$9,278/QALY (with increased event utility decrements). For event costs, the ICER varied between Can$14,491/QALY and

Can$9,448/QALY with a variation of 25% around the base-case cost values. Varying the utility of stable CHD (baseline utility) by 15% around the base-case value resulted in the ICER varying from Can$10,187 to Can$14,506. ICERs varied from Can$13,537/QALY to Can$10,905/QALY if all mortality multipliers were increased or decreased simultaneously by 2 SE from their base-case value. Model output showed little sensitivity to the discount rate and the CABG weight (i.e., the proportion of revascularizations that are CABG). The model was not sensitive to a 10% variation in age, gender, and event specific 1-year post-event mortality rates. Probabilistic sensitivity analysis predicted that the likelihood that the ICER would be below Can$50,000/QALY was 98.1% for the lifetime model horizon (Figure 3). That is, only 19 out of 1000 simulations resulted in an ICER of above Can$50,000/QALY. For the 10-year horizon this probability was 99.8% and for the 5-year model it was 99.5%.

If the willingness to pay to gain one QALY is Can$50,000, the probability that atorvastatin 80 mg is cost-effective is 98.1% (Figure 4). For a willingness to pay of Can$70,000 per QALY gained, the probability of atorvastatin 80 mg being cost-effective rises to 98.8% (i.e., only 12 of 1000 probabilistic sensitivity analysis simulations gave an ICER above Can$70,000 per QALY).

FIG. 2 Deterministic sensitivity analysis for the lifetime horizon. CABG: coronary artery bypass grafting; CHD: coronary heart disease; CHF: congestive heart failure; DA: documented angina; MI: myocardial infarction; PAD: peripheral artery disease; QALY: quality adjusted life year; RCA: resuscitation after cardiac arrest; Revasc: revascularization; SE: standard error; TIA; transient ischemic attack

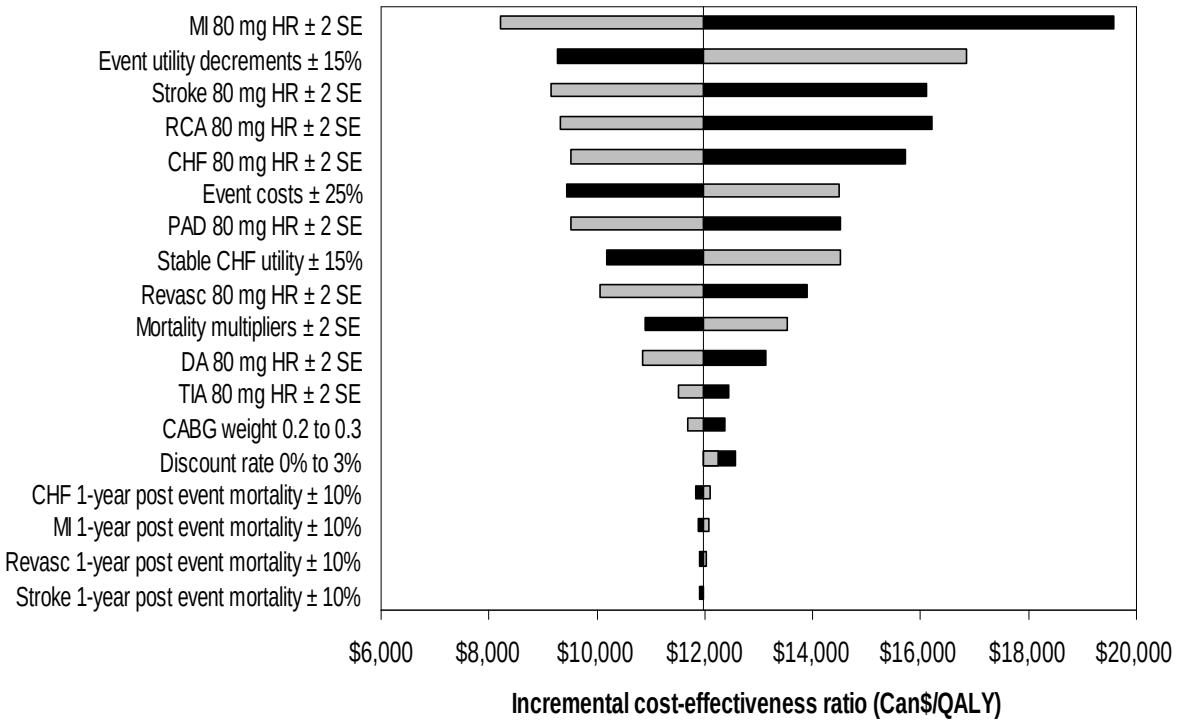


FIG. 3 Probabilistic sensitivity analysis - lifetime horizon. The line indicates the Can$50,000/QALY threshold. QALY: quality-adjusted life year.

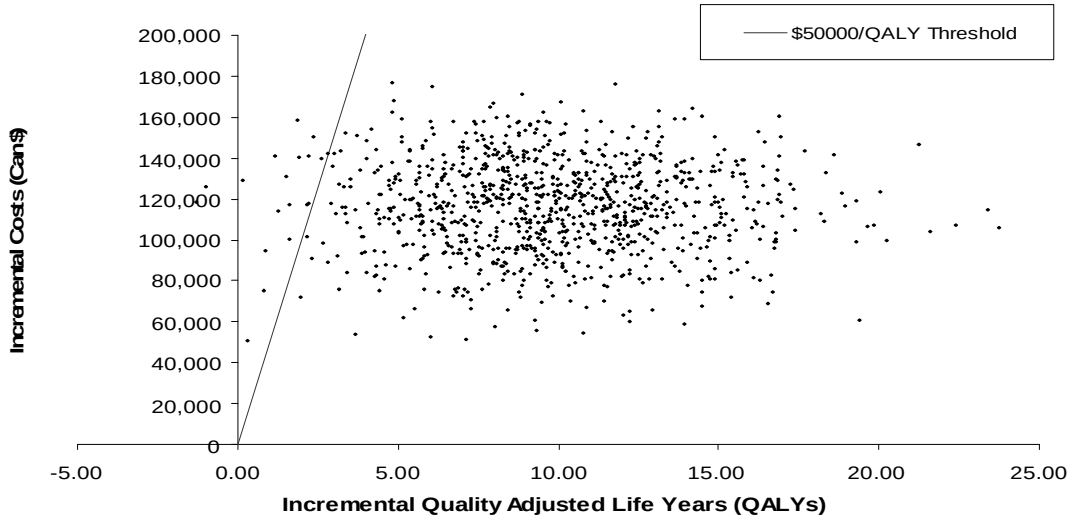
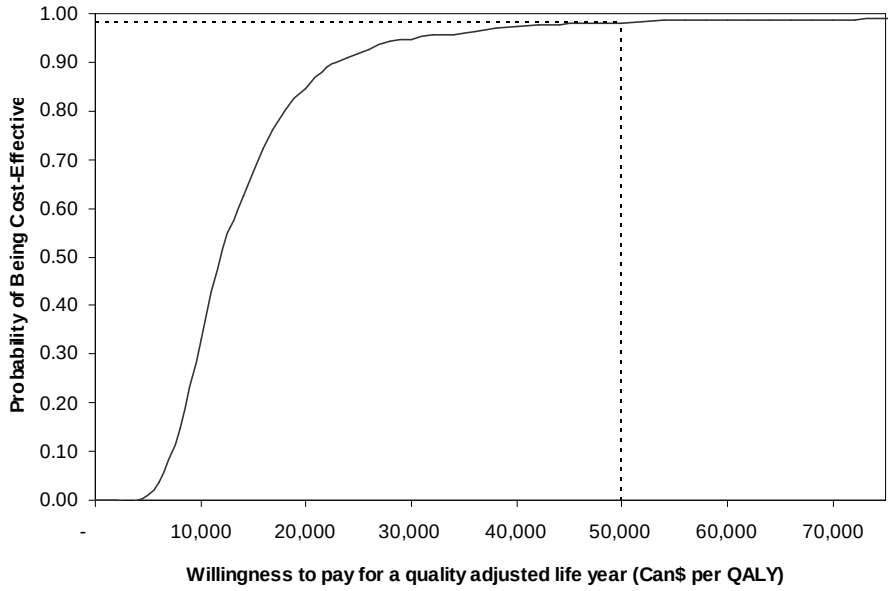


FIG. 4 Cost-effectiveness acceptability curve indicating the proportion of simulations that result in a cost-effective value from a willingness to pay Can$50,000 to gain a QALY. QALY: quality-adjusted life year.



DISCUSSION

This study predicts that the treatment of Canadian CHD patients with intensive lipid lowering therapy using 80 mg of atorvastatin per day may be cost-effective compared to treatment with the lower dose of 10 mg of atorvastatin per day from the perspective of the Canadian Ministries of Health.

The results of this study are in agreement with two recently published economic analyses of 80 mg atorvastatin versus 10 mg atorvastatin, both of which were based on the TNT trial.[34,35] Adapting the same model as used in this study to local parameters, Taylor et al.[34] arrived at a lifetime incremental cost per QALY gained of €9,500 in the UK, €21,000 in Spain and €15,000 in Germany, which is comparable to the ICER reported here. Mark et al.[35] reported an incremental cost (including event-related hospitalization costs and study drugs) per primary endpoint prevented of US$8,964 over a mean of 4.9 years based on a prospective economic substudy of 5,308 US patients enrolled in the TNT trial.

Lipid-lowering using statins versus no treatment was previously shown to be cost-effective in Canada for both primary and secondary prevention.[14-17] The ICERS for secondary prevention compared to no treatment, depending on the type of statin, age, and the number of risk factors, ranged from Can$14,128/life year gained to Can$47,778/life year gained for men, and between Can$18,217 and Can$114,614 for women (1996).[14] Another study used data provided by the Canadian Heart Health Survey to estimate the risk of CVD in a random sample of the Canadian population.[15] A cost-effectiveness ratio for treatment with simvastatin versus no treatment was calculated for each individual in the sample. Treatment with simvastatin for secondary prevention was found to be cost-effective at less than Can$50,000/life year gained (1996) for 99.8% of men and 86.1% of women. The Markov model presented here resulted in an ICER of Can$9,667 per QALY gained over a lifetime horizon. The probability that the ICER will be below a threshold of Can$50,000 per QALY was above 98%. The ICER for a 10-year horizon was reduced to Can$1,366 per QALY and for the 5-year horizon, the 80 mg atorvastatin per day treatment was dominant. These ICERs are similar to those reported in other economic evaluations of statin treatment in secondary prevention. Results from this study must be viewed in the light of its limitations. Ideally, the US utility values used in the model would be replaced with Canadian values. In addition, utility values for coronary artery bypass graft and percutaneous transluminal coronary angioplasty were assumed to be the same value as for stable coronary heart disease. This may result in an underestimate of the utilities in these patients as these procedures may actually increase quality of life. However, since the model was only moderately sensitive to variation in utility values, there should not be a significant impact on the results generated.

The LDL-C level for patients at the start of the TNT trial was required to be lower than 3.4 mmol/L. In clinical practice, patients may present with higher LDL-C levels. In the CALIPSO study, a cross-sectional observational study of statin therapy in Canadian patients with hypercholesterolemia, the mean LDL-C prior to statin treatment was 4.3 mmol/L.[36] It is possible that the hazard ratios for patients with very high LDL-C levels, treated with either dose of atorvastatin, may differ from those described in the TNT trial.

The costs for major and minor events were based on the OCCI 2006-2007 acute inpatient cost data,[30] and include the total cost of hospitalization due to that event including overhead (indirect hospital costs). Hospitalization costs will vary across Canada resulting in variations in cost-effectiveness by region. In addition, only acute event costs were taken into consideration; other costs including rehabilitation, home care, and loss of productivity may also have an impact on the cost-effectiveness of intensive versus moderate lipid lowering. However, there should not be a significant impact on the results, since the model was only moderately sensitive to variations in event costs. Lipitor™ will no longer be under patent in Canada in July 2010, which may result in a reduction in drug price; this would lead to an increase in the cost-effectiveness of the 80 mg atorvastatin treatment.

Adverse experiences were not included in this study; however, in the TNT study more

patients allocated 80 mg of atorvastatin experienced treatment related adverse events such as myalgia, diarrhea, nausea and abdominal pain, than those allocated 10 mg of atorvastatin (8.1% vs. 5.8%, $P<0.001$, respectively).[12] These types of adverse events do not usually require costly therapies and as such are unlikely to have a significant impact on results generated by the model. More patients randomized to atorvastatin 80 mg than to atorvastatin 10 mg discontinued treatment (7.2% vs. 5.3%, $P<0.001$).[12] Two recent studies of patients receiving statins in Quebec suggest that in a clinical practice setting compliance rates may be lower than in clinical trials,[37,38] but no data is available comparing compliance rates between high- and low-dose statins. Non-compliance is known to be associated with higher cardiovascular event rates and mortality than good compliance.[39,40] Patients were assumed to continue with their original atorvastatin dosages throughout the model. This may not reflect a 'real life' scenario; since in clinical practice patients may switch dosages or use a different statin.[41]

Another limitation of this study is that the TNT trial population was not representative of the Canadian population with established CHD. The trial population was mostly male, and only 18 % of the trial population were older than 70 years. Results of this study can therefore only be reliably applied to populations similar to those in the TNT trial.

Strengths of the model presented here include the use of a head-to-head trial as opposed to placebo controlled trials used in previous studies, and the use of a 5-year trial with data on clinical endpoints such as MI and stroke, rather than the use of surrogate endpoints such as LDL-C reduction data collected over a short time period. Other strengths include the use of Canadian mortality rates to estimate first year post-event mortality rates and the use of Canadian data on revascularization practices (i.e., the relative proportion of CABG vs. PCI).

CONCLUSIONS

From the perspective of the Canadian Ministries of Health, intensive lipid lowering therapy with patients with 80 mg of atorvastatin per day may be cost-effective versus 10 mg of atorvastatin per day in patients with stable CHD.

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Disclosures

Monika Wagner and Mireille Goetghebeur are employed by Biomedcom Consultants Inc. Elizabeth Merikle was employed by Pfizer, Canada at the time of this study; she is now employed by United BioSource, Canada. Douglas CA Taylor is employed by i3 Innovus, in addition, he has worked as a paid consultant for Pfizer. Ankur Pandya, Paula Chu were also employed by i3 Innovus at the time of this study; they have subsequently returned to Harvard to continue their studies.

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